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BINGHAM MCCUTCHEN LLP
Three Embarcadero Center
San Francisco, CA 94111-4067

EXAMINER	
YOUNG, MICAH PAUL	
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DAVID FIKSTAD and KANYI QUAN

Appeal 2008-3445
Application 09/871,318
Technology Center 1600

Decided: August 27, 2008

Before DEMETRA J. MILLS, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to methods, pharmaceutical formulations, and devices for the transdermal delivery of lasofoxifene. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm in part and enter a new ground of rejection.

BACKGROUND

"Naturally occurring estrogens and synthetic compositions demonstrating 'estrogenic' activity are useful for various therapeutic applications" (Spec. 1). "Lasofoxifene (CP-336,156) is a selective estrogen receptor modulator (agonist/antagonist). It has been shown to have similar therapeutic effects in bone and LDL levels to estradiol but without the uterine-stimulating effects associated with estradiol therapy" (*id.* at 2).

"Transdermal delivery of drugs provides many advantages over conventional oral administration. Advantages of transdermal systems include convenience, uninterrupted therapy, improved patient compliance, reversibility of treatment (by removal of the system from the skin), elimination of 'hepatic first pass' effect, a high degree of control over blood concentration of the drug, and improved overall therapy" (*id.* at 3).

The Specification discloses "methods, pharmaceutical formulations, and devices for the transdermal delivery" of lasofoxifene (*id.*).

DISCUSSION

1. CLAIMS

Claims 3-5, 14, 17-19 and 22-40 are pending and on appeal. Claims 3, 14, 17, 30, 32 and 36 are representative and read as follows:

Claim 3: A transdermal formulation comprising an adhesive drug matrix reservoir and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

Claim 14: A device for administering an active agent to the skin or mucosa of an individual comprising a laminated composite of

a. a backing layer defining an upper portion of a reservoir and extending to the periphery of a peel seal disk;

b. an active agent-permeable membrane extending to the periphery of the peel seal disk and the backing layer, and underlying the backing layer, the backing layer and membrane defining;

c. the reservoir therebetween that contains a transdermal formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof;

d. the peel seal disc underlying an active agent-permeable membrane;

e. a heat seal about the periphery of the peel seal disc, the active agent-permeable membrane and the backing layer;

f. an adhesive overlay having a central portion overlying the backing layer and a peripheral portion that extends beyond the periphery of the peel seal disc; and

g. a removable release liner underlying the peripheral portion of the adhesive overlay and the peel seal disc.

Claim 17: A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with an effective pharmaceutical formulation of any of claims 3 to 5.

Claim 30: [A transdermal device comprising a means for adhering a drug reservoir to the application situs and the transdermal formulation of any of claims 3 to 5, and an effective amount of a drug permeation enhancer], wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

Claim 32: A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a free form hydroalcoholic gel and an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

Claim 36: A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with a transdermal formulation comprising a liquid reservoir drug formulation comprising an effective amount of lasofoxifene or a pharmaceutically acceptable salt thereof.

2. OBVIOUSNESS

Claims 3-5, 14, 17-19 and 22-40 stand rejected under 35 U.S.C. § 103 as obvious in view of Cormier[1] and Ke.[2] The claims have been argued in six groups: claims 3-5, 28, 29, and 40 (group 1); claims 30 and 31 (group 2); claims 14, 18, 19, and 25-27 (group 3); claims 17 and 22-24 (group 4); claims 32-35 (group 5); and claims 36-39 (group 6). The claims in each group stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii).

With regard to claim 3, the Examiner relies on Cormier for disclosing "a transdermal formulation comprising an adhesive matrix reservoir" (Ans. 3). The Examiner finds that Cormier discloses that the "transdermal formulation delivers various active agents including antiestrogen and antiosteoporotic agents such as tamoxifen and raloxifene" but "lacks a disclosure of lasofoxifene" (*id.* at 4).

The Examiner relies on Ke as disclosing a combination of "active agents in a transdermal … including lasofoxifene" (*id.*, citing Ke at claim 1). The Examiner also relies on Ke as disclosing that droloxifene, raloxifene and tamoxifen can be used in the disclosed combination therapy in place of lasofoxifene (*id.*).

The Examiner concludes that it "would have been obvious to include the lasofoxifene" of Ke into the device of Cormier "since they comprise similar components, and are within the same field of endeavor" (*id*). The Examiner further concludes that it "would have been obvious to make the simple substitution and combination with an expected result of a viable

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[1] Cormier et al., US 6,203,817 B1, Mar. 20, 2001
[2] Ke et al., US 6,323,232 B1, Nov. 27, 2001

transdermal device useful in treating various estrogen related disorders" (*id.* at 4-5).

We conclude that the Examiner has set forth a prima facie case that claim 3 would have been obvious to the ordinary artisan. Cormier discloses "compositions, devices, and methods for transdermal administration of non-zwitterionic drugs … wherein the compositions and devices are provided with a salt of a non-zwitterionic drug" (Cormier, col. 5, ll. 20-25). Cormier discloses that the device "may be a passive transdermal device known in the art" (*id.* at col. 5, ll. 55-57). Cormier also discloses that examples of drugs to be administered include "antiestrogen such as tamoxifen; and antiosteoporotic agents such as raloxifen [sic]" (*id.* at col. 7, ll. 66-67). Cormier discloses that the matrix reservoir for the drug may be a pressure sensitive adhesive (*id.* at col. 9, l. 61).

Ke discloses "[p]harmaceutical combination compositions including certain estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists … useful for the treatment of bone disorders including osteoporosis" (Ke, abstract); preferred estrogen agonists/antagonists include raloxifene and tamoxifen (*id.* at col. 3, l. 49). Ke also discloses a "pharmaceutical composition comprising synergistic effective amounts of lasofoxifene and PGE2 in a pharmaceutically acceptable carrier" (Ke, claim 1). Ke also discloses transdermal dosage forms (*id.* at col. 37, ll. 49-52).

We agree with the Examiner that it would have been prima facie obvious to one of skill in the art to combine the teachings of Cormier and Ke and thereby arrive at the invention of claim 3. Ke teaches that lasofoxifene formulations may be administered transdermally and that lasofoxifene is an

estrogen agonist/antagonist comparable to raloxifene and tamoxifen. Cormier teaches that a matrix reservoir for transdermal administration of raloxifene and tamoxifen (among other things) may be a pressure sensitive adhesive. Thus, it would have been obvious to one of skill in the art to administer lasofoxifene, like raloxifene and tamoxifen, transdermally via an adhesive drug matrix reservoir.

Appellants argue that "one of ordinary skill in the art would not be motivated to combine the publications" because the lasofoxifene, raloxifene, and tamoxifen "would be expected to have dramatically different chemical properties requiring unique formulations" and that

> the differing chemical structures and properties of tamoxifen and raloxifene as compared to lasofoxifene actually *teach away* from combining lasofoxifene with the transdermal delivery system discussed in Cormier *et al*. because the compounds are so structurally different that one of ordinary skill would not reasonably expect them to behave in the same manner … when formulated into a drug matrix.

(App. Br. 15-16).

We are not persuaded by this argument. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 1740.

Although the raloxifene and tamoxifen disclosed in Cormier are structurally different than Ke's lasofoxifene, Ke expressly suggests transdermal administration of a composition that can contain lasofoxifene

(Ke, claim 1), raloxifene or tamoxifen (*id.* at col. 3, l. 49). Cormier describes an adhesive drug matrix reservoir for the transdermal administration of compounds including raloxifene and tamoxifen (Cormier, col. 7, ll. 66-67). The evidence therefore shows that it would be well within the skill of one in the art to formulate the lasofoxifene of Ke in Cormier's matrix for transdermal administration. The combination of the lasofoxifene of Ke with the adhesive drug matrix reservoir of Cormier appears to be nothing more than the combination of old elements for their expected function to yield predictable results.

With regard to claim 17, Appellants argue that "the Examiner has failed to show how the cited publications disclose or suggest the methods of treatment and prevention" (App. Br. 17).

We are not persuaded by this argument. As set forth above, the combination of Ke and Cormier would have made obvious the transdermal formulation of claim 3 that contains lasofoxifene. Ke discloses that the disclosed compositions are useful for treating osteoporosis (Ke, col. 3, ll. 37-42). Ke also discloses that "[w]omen experience a sharp acceleration of bone loss immediately following menopause" and that "[e]strogen is the agent of choice in preventing osteoporosis or post menopausal bone loss in women" (Ke, col. 1, ll. 31-37). Thus, one of skill would understand that osteoporosis is a disease associated with estrogen deficiency or disregulation and that the suggested lasofoxifene transdermal formulation would be useful in treating osteporosis. Ke and Cormier therefore would have suggested the method of claim 17 to a person of ordinary skill in the art.

With regard to claim 30, Appellants argue that "the Examiner has not cited any publication describing an effective amount of a cell-envelope disordering compound … nor how a method using such a compound would be obvious" (App. Br. 19, emphasis omitted).

We are not persuaded by this argument. The Specification provides several examples of cell-envelope disruptors; they include isopropyl myristate, methyl laurate, etc. (Spec. 7, ll. 16-19). Originally filed claim 10 specifies that cell-envelope disordering compounds also include "a lower alkanol." Thus, we interpret the term "cell envelope disordering compound" to include at least lower alkanols and the compounds listed in the Specification as cell-envelope disruptors.

Cormier discloses, as recognized by the Examiner (Ans. 8), that propylene glycol is a component of its transdermal formulations (e.g. Cormier, Examples 1, 2, and 4). Thus, the combination of Cormier and Ke would have suggested to one of skill in the art the formulation of lasofoxifene with propylene glycol. Another name for propylene glycol is propane-1,2-diol. When we give the claim term "cell-envelope disordering compound" its broadest reasonable interpretation in light of the Specification, we conclude that "lower alkanol" reasonably appears to encompass propane-1,2-diol; i.e., propylene glycol. Therefore, we agree with the Examiner that the cited references would have suggested lasofoxifene formulated with a cell envelope disordering compound.

With regard to claim 14, Appellants argue that "the Examiner has not cited any publication describing claim elements such as the peel seal disc underlying the active agent permeable membrane, the heat seal about the

periphery of the peel seal disc and the removable release liner" (App. Br. 21, emphasis omitted).

We agree with Appellants that the Examiner has not adequately explained why a device meeting all the limitations of claim 14 would have been obvious to a person of ordinary skill in the art based on Cormier and Ke. The Examiner relies on element 24 of Cormier's device as "act[ing] as a protective peel seal disk in the transdermal device" (Ans. 7). Cormier, however, describes element 24 as a "strippable release liner" (Cormier, col. 9, ll. 56-58). Claim 14 requires both a release liner (claim 14, part g) and a peel seal disc (claim 14, part d). The release liner underlies the peel seal disc; thus, the two claim elements cannot be met by a single element in the prior art device. The rejection of claims 14, 18, 19, and 25-27 is reversed.

With regard to claim 32, Appellants argue that the "Examiner has not cited any publication describing a transdermal formulation comprising a free form hydroalcoholic gel" (App. Br. 23, emphasis omitted).

We are not persuaded by this argument. The Specification does not define "hydroalcoholic gel" but describes "**Free Form Hydroalcoholic Gel Preparation**" as being prepared by mixing ethyl alcohol, water, glycerin, enhancer, drug, and gelling agent (Spec. 12, ll. 4-8). Thus, we interpret the term hydroalcoholic gel to mean a gel containing alcohol and water.

Cormier discloses transdermal formulations that are aqueous gels that contain ethanol (e.g. Cormier, Examples 1, 2, and 4). Cormier further discloses that the drug reservoir can be formed of a rubbery polymer or an aqueous gel (*id.* at col. 9, ll. 28-31). Thus, the combination of Cormier and

Ke would have suggested to one of skill in the art lasofoxifene formulated in a free form hydroalcoholic gel.

With regard to claim 36, Appellants argue that "the Examiner has not cited any publication describing a transdermal delivery device comprising liquid reservoir drug formulation" (App. Br. 24-25, emphasis omitted).

We are not persuaded by this argument. The Specification provides that a "matrix patch is distinguished from a 'liquid reservoir patch,' wherein an active permeant or drug is dissolved in a gelled liquid" (Spec. 6, ll. 11-13). Thus, we interpret the term "liquid reservoir" to encompass a reservoir in gel form. As discussed above, Cormier discloses transdermal formulations that are gelled liquids. Thus, the combination of Cormier and Ke would have suggested to one of skill in the art lasofoxifene formulated in a liquid reservoir form (i.e., a gelled liquid form).

NEW GROUND OF REJECTION

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following new ground of rejection: claims 14, 18, 19, and 25-27 are rejected under 35 U.S.C. § 103 as obvious in view of Ebert,[3] Cormier, and Ke. Ebert teaches the device defined by claim 14 (Ebert, Fig. 1 and col. 2, l. 60 to col. 3, l. 10) but does not expressly suggest using the device to administer lasofoxifene. Cormier and Ke suggest administering lasofoxifene transdermally for the reasons discussed at length above. It would have been obvious to a person of ordinary skill in the art to combine Ebert's device with the transdermal administration of lasofoxifene suggested by Cormier and Ke because Ebert states that the disclosed device is useful for administering a variety of

[3] Ebert et al., U.S. Patent 5,662,925, issued Sept. 2, 1997.

agents, including estradiol (Ebert, col. 4, l. 20). Combining the cited references thus amounts to "the predictable use of prior art elements according to their established functions." *KSR*, 127 S Ct. at 1740. The additional limitations of claims 18, 19, and 25-27 would have been obvious for the reasons discussed above with respect to claims 17 and 30.

SUMMARY

We affirm the rejection of claims 3-5, 17, 22-24, and 28-40 under 35 U.S.C. § 103. We reverse the rejection of claims 14, 18, 19, and 25-27 as obvious in view of Cormier and Ke. We enter a new ground of rejection of claims 14, 18, 19 and 25-27.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review.

37 CFR § 41.50(b) also provides that the Appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner . . . .

(2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record . . . .

AFFIRMED-IN-PART, 37 C.F.R. § 41.50(b)

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BINGHAM MCCUTCHEN LLP
Three Embarcadero Center
San Francisco CA 94111-4067